ADVANCES IN CAR T-CELL THERAPY

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DISCLOSURES

Advances in CAR T-cell Therapy

Iris Isufi, MD, has affiliations with Astra Zeneca, Celgene, Kite Pharmaceuticals and Novartis (C*onsultant*)**.**

BEATING CANCER IS IN OUR BLOOD.

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Objectives

- Why CAR T-cell (chimeric antigen receptor T-cell) therapy shows promise for blood cancers
- Approved and emerging CAR T-cell therapies
- Side effects of CAR T-cell therapy: what to expect
- The future of CAR T-cell therapy for blood cancer patients

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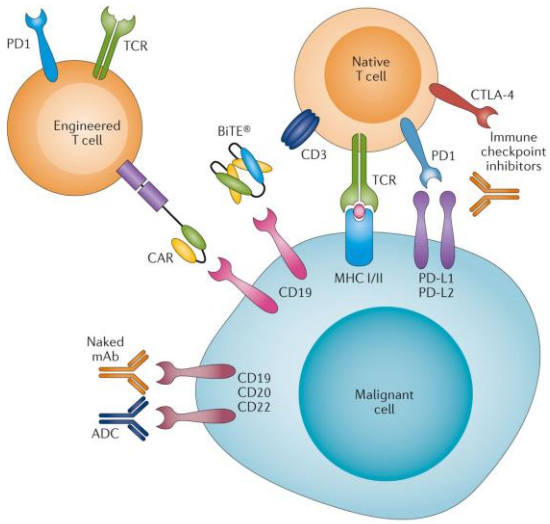
Multiple Mechanisms of Modulating Immune System to Treat Cancer

- Monoclonal antibodies or antibody drug conjugates
- Dual antigen re-targeting proteins
- Immune checkpoint antibodies
- Chimeric antigen receptor T cells



Batlevi, C. L. et al, Nat. Rev. Clin. Oncol, 2015

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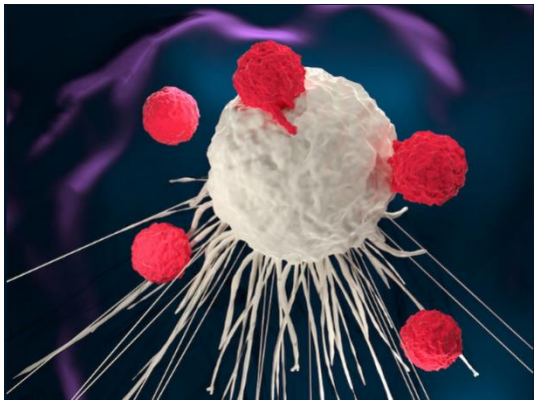
What is CAR T-cell therapy?

CAR T-cell therapy is a type of cancer therapy that uses a patient's own modified white blood cells to kill cancer cells.



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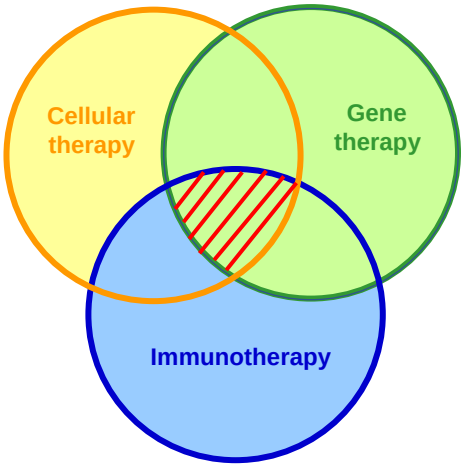
CAR T-Cells are at The Intersection of Three Innovative Technologies



Cellular therapy
Using the patient's own T- cells as therapy

Gene therapy
Insertion of genes into a patient's cells, thereby causing these cells to produce a new therapeutic protein (CAR)

Immunotherapy
Harnessing the patient's own immune system (T- cells) to treat his/her disease

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Tragedy, Perseverance, and Chance — The Story of CAR-T Therapy

The emergence of CAR-T therapy, like most scientific advances, reflects the incremental insights of hundreds of scientists over decades. Indeed, the story of CAR-T therapy says as much about the methodical nature of scientific progress as it does about the passions that sustain it.

Lisa Rosenbaum, M.D.

N Engl J Med 377;14 nejm.org October 5, 2017

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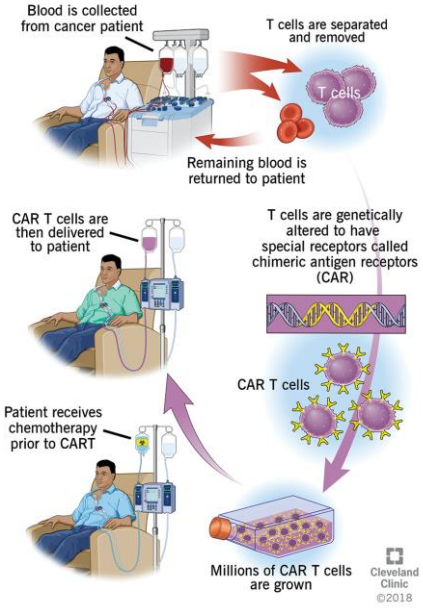
From Manufacturing of CAR T-Cells to Infusion



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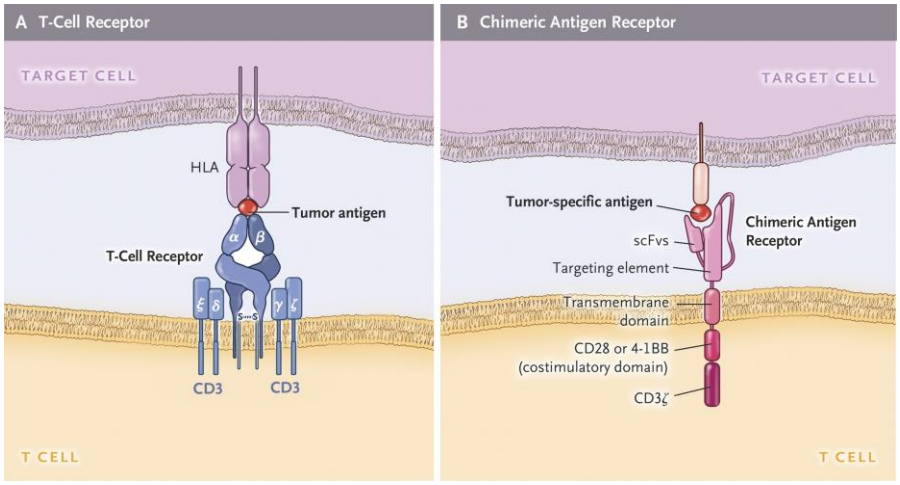
Structure of T-Cell Receptors and CAR Modified T-cells



June CH, Sadelain M. N Engl J Med 2018;379:64-73

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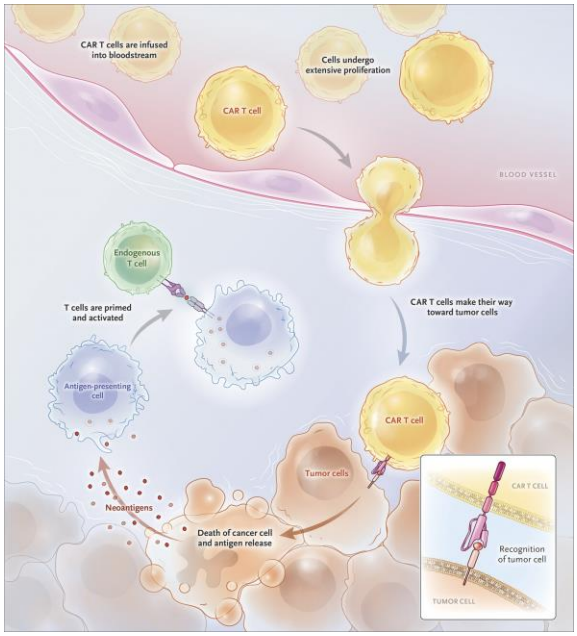
CAR T Cells Traffic to Tumor and Proliferate Extensively after Infusion



June CH, Sadelain M. N Engl J Med 2018;379:64-73

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Ideal CAR Target

- Tumor specific antigen (Ag)
  - Required for tumor pathogenicity (ability to cause disease)
  - Critical for survival, such that loss of that Ag comes at really high cost for the cancer
- Highly expressed on all tumor cells (cancer stem cells?)
  - Cell surface molecule
- Absent from normal tissue (or where normal tissue is dispensable)
- Absent from T cells (to avoid self killing)

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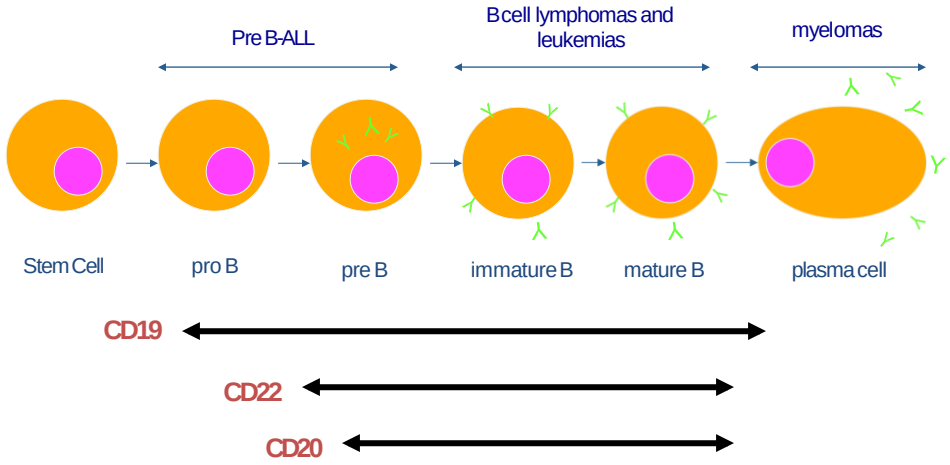
CD19 as a Target of B-Cell Malignancies



CD19 expression is generally restricted to B cells and B-cell precursors and, importantly, is expressed by most B-cell malignancies, and represents a rational target for therapy

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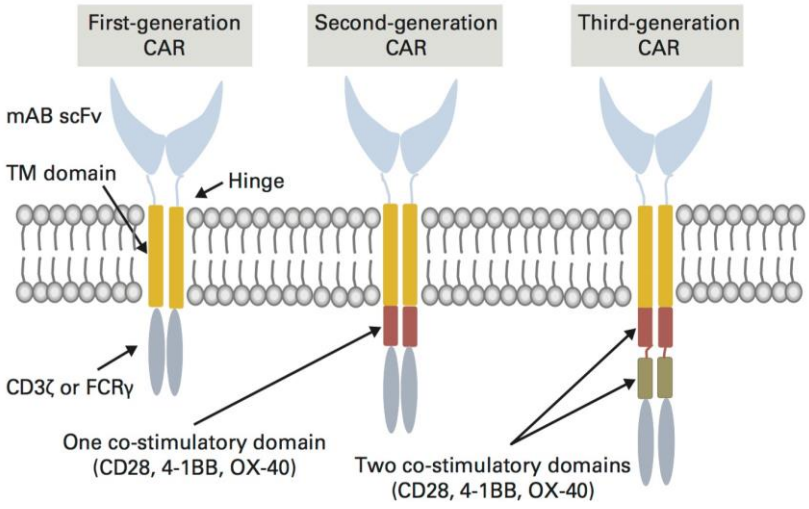
Evolution in CAR Design



Park Jet al. *JClin Oncol*. 2015;33(6):651-653.

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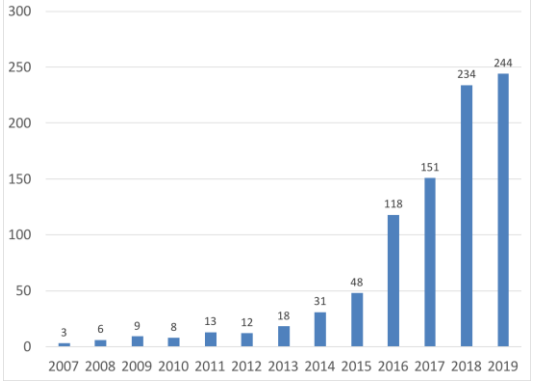
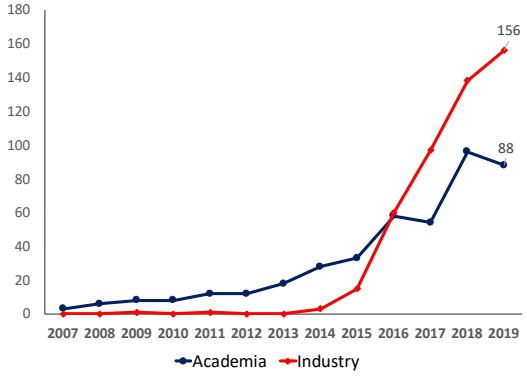
Total Registered CAR-T Trials Worldwide





Industry is Taking Over CAR T-Cell Development

Data source: CellTrials.org

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Selected Approved or Late-Stage CAR T Therapies

Drug name	Company	Indication	Target
Marketed			
Tisagenlecleucel (CTL-019)	Novartis	Childhood B-cell ALL (≤25) Adult DLBCL, transformed FL (tFL)	CD19
Axicabtagene ciloleucel (KTE-C19)	Gilead Sciences (Kite Pharma)	DLBCL, tFL and PMBCL	CD19
Brexucabtagene autoleucel (KTE-X19)	Gilead Sciences (Kite Pharma)		
Phase III			
Lisocabtagene maraleucel (JCAR 017)	Celgene (Juno Therapeutics)	B-NHL	CD19
Idecabtagene vicleucel (bb2121)	Bluebird bio/Celgene	Multiple myeloma	BCMA

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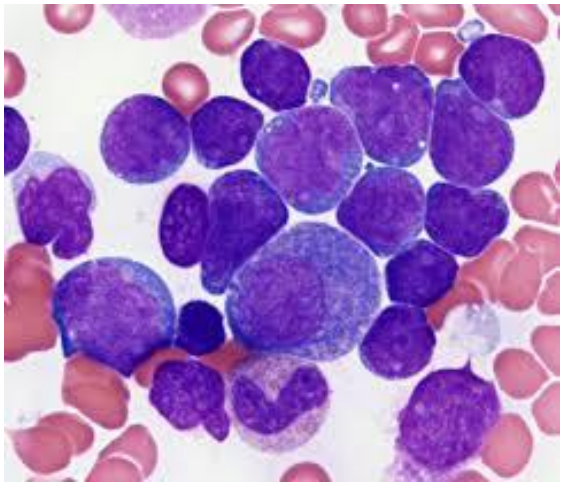
CAR T- Cell Therapy in B-Cell Acute Lymphoblastic Leukemia (B-ALL)



Atlas of Genetics and Cytogenetics in Oncology and Hematology

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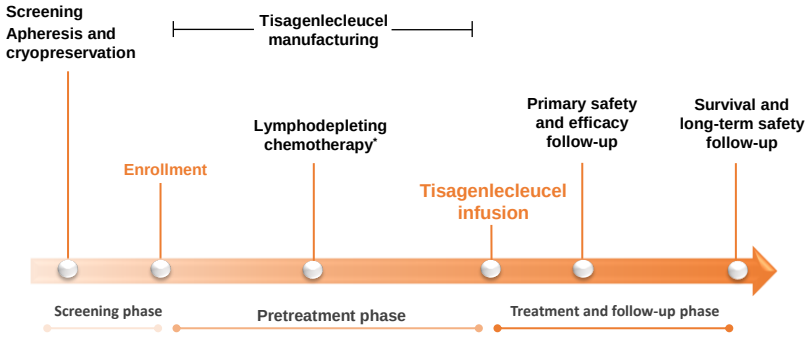
Pediatric Relapsed/Refractory (R/R) B-ALL: ELIANA Study Design

- ELIANA (NCT02435849) is a phase 2, open-label, single-arm study in pediatric and young adult patients with r/r B-cell ALL[1-2]



B-cell ALL, B cell acute lymphoblastic leukemia.

*To be completed 2 to 14 days prior to Tisagenlecleucel infusion.

1. Buechner J, et al. *Haematologica*. 2017;102(suppl 2) [abstract S476];
2. Maude SL, et al. *N Engl J Med.* 2018;378:439-448;

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ELIANA Study in B-ALL

- Single arm, open-label, multi-center, global phase 2 study
  - 107 pts screened, 88 enrolled, 68 treated
- Dose of Tisagenlecleucel: 2-5 x 10^6 CAR-T cells/kg
  - Conditioning chemo: Flu 30 mg/m2 x 4days + Cy 500 mg/m2 x 2 days
- Response rates: Complete Remission/Complete Remission with incomplete hematologic recovery **CR/CRi: 81%** (CR 60% + CRi 21%)
- **Tisagenlecleucel approved for treatment of patients up to age 25 with B-ALL that is refractory or in 2nd or later relapse**

1. Buechner J, et al. *Haematologica*. 2017;102(suppl 2) [abstract S476];
2. Maude SL, et al. *N Engl J Med.* 2018;378:439-448;

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ELIANA: Patient Demographics and Baseline Clinical Characteristics

Characteristics	Patients (N = 75)
Age, median (range), years	11 (3-23)
Prior stem cell transplant, n (%)	46 (61)
Previous line of therapies, median (range), n	3 (1-8)
Disease status, n (%)	
Primary refractory	6 (8)
Chemo-refractory or relapsed	69 (92)
Morphologic blast count in bone marrow, median (range), %	74 (5-99)

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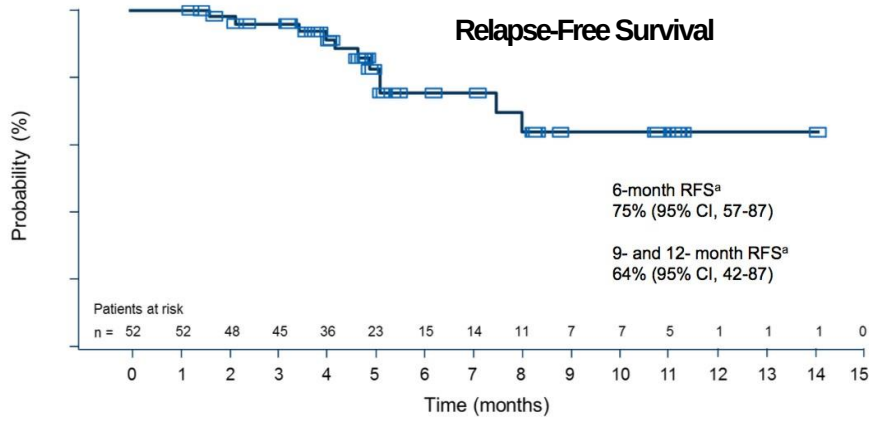
Duration of Remission: ELIANA



Patients (N = 52) Number of events (n = 11) Median follow-up, 4.8 mo
Median DOR, not reached

Buechner Jet al. *EHA 2017*, Abstract S476

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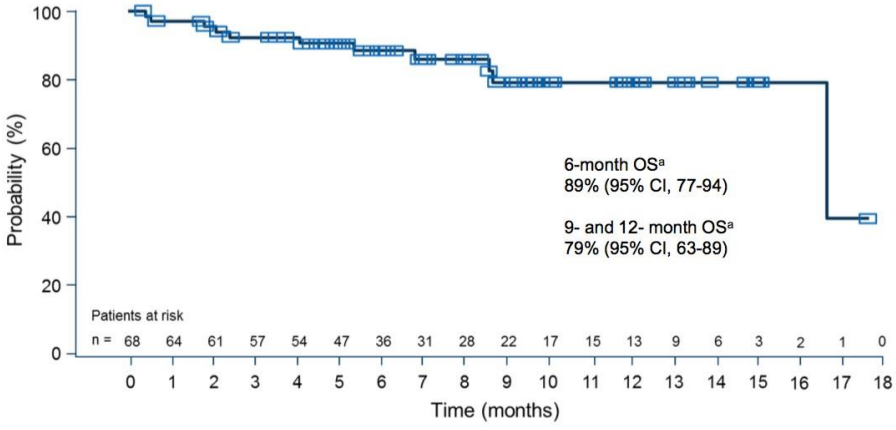
Overall Survival: ELIANA



Patients (N = 68)

Number of events (n = 11)

Median follow-up, 6.2 mo (max, 17.6 mo)
Median OS, 16.6 mo

Buechner Jet al. *EHA 2017*, AbstractS476

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ELIANA: Overall safety of Tisagenlecleucel

Event	Any Time (N=75)	≤8 Wk after Infusion (N=75)	>8 Wk to 1 Yr after Infusion (N=70)
		number of patients (percent)	
Adverse event of any grade	75 (100)	74 (99)	65 (93)
Suspected to be related to tisagenlecleucel	71 (95)	69 (92)	30 (43)
Grade 3 or 4 adverse event	66 (88)	62 (83)	31 (44)
Suspected to be related to tisagenlecleucel	55 (73)	52 (69)	12 (17)

Maude SL, et al. *N Engl J Med.* 2018;378:439-448

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Outcomes with CART19 Therapy in Children and Adults with Relapsed/Refractory B-ALL

Reference	CAR	Population	Response
Maude et al. NEJM 2018	PENN 4-1BB	ALL (peds/adults) N=71	CR: 81% 6mo EFS & OS: 73% & 90% 12mo EFS & OS: 59% & 76% 11% proceeded to alloHSCT after CAR T cells
Park J et al. ASCO 2017, Abstract 7008	MSKCC CD28	ALL (adults) N=53	CR: 84.6% MRD-CR rate: 66.6% 39% proceeded to alloHSCT after CAR T cells.
Turtle et al. JCI 2016	Seattle 4-1BB Defined CD4/CD8 composition	ALL (adults) N=30	CR=93% MRD-CR rate: 86% 1 pt proceeded to alloHSCT after CAR T cells
Lee et al. Lancet 2015	NCI CD28	ALL (peds/adults) N=21	CR=67%

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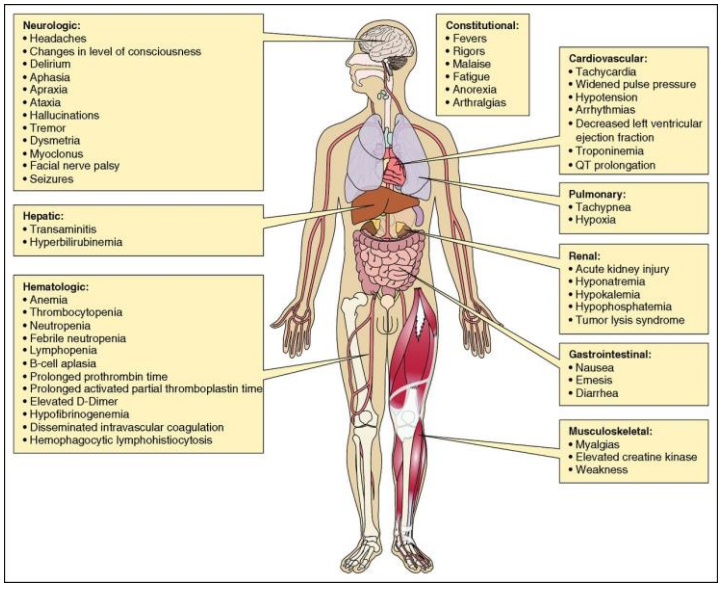
CAR-T 19 Associated Toxicities



Professional illustration by Patrick Lane, ScEYEnce Studios

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CAR-T 19 Associated Toxicities

- Cytokine Release syndrome (CRS)
  - Fevers, flu-like syndrome, low blood pressure, difficulty breathing
- Neurologic changes (NT, CRES, ICANS)
  - Headaches, tremors, mental status changes, difficulty speaking, rarely seizures (normal MRI)
- Organ toxicity (liver, kidneys)
- Off tumor/On target: B cell aplasia
  - Prolonged; Cases requiring IVIG repletion
- Toxicities are usually manageable and reversible

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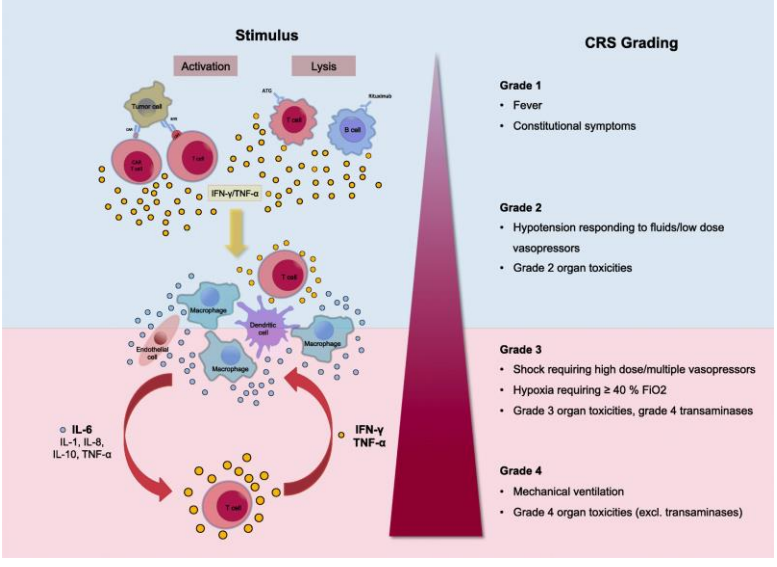
Mechanism of Cytokine Release Syndrome (CRS)



Shimabukuro-Vornhagen, A., Gödel, P., Subklewe, M. *et al.* Cytokine release syndrome. *j. immunotherapy cancer* **6,** 56 (2018)

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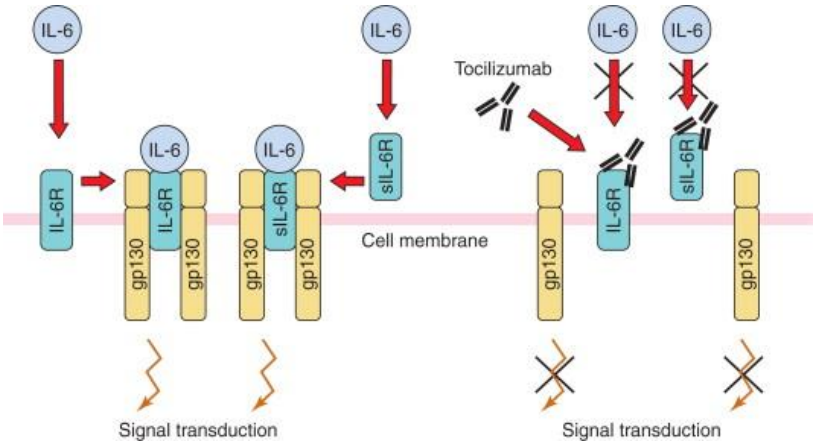
Inhibitory Action of Tocilizumab in IL-6 Signaling



Norihiro Nishimoto, Toru Mima, in *Rheumatoid Arthritis*, 2009

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Neurologic Toxicity with CAR T-Cells

- Symptoms and signs: headaches, tremors, somnolence, speech difficulty, confusion, paralysis of limbs, rarely seizures, etc.
  - 1st phase (Days 0-5) – symptoms may appear with other CRS symptoms
  - 2nd phase (After day 5) – starts after CRS symptoms have subsided
- Neurotoxicity typically lasts 2-4 days but may vary in duration from few hours to few weeks. It is generally reversible.
  - Corticosteroids treatment of choice in managing neurotoxicity.
  - Seizure prophylaxis is recommended with levetiracetam (750 mg oral/IV q 12 hrs) from day 0 to day 30.

Neelapu, SS, et al. *Nature Reviews Clinical Oncology*, *15*(1), 47-62.

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Mechanism of Neurotoxicity

- Pathophysiology remains unclear:
  - Diffusion of cytokines into central nervous system
  - Trafficking of T cells into central nervous system
- CSF is usually positive for CAR T cells
- MRI of brain is usually negative
  - Reversible white matter changes and cerebral edema have been rarely observed
- EEG is either non-focal with generalized slowing or might show non-convulsive seizure pattern

Maude et al. NEJM 2014; Davila et al. SciTrMed 2014; Lee et al. The Lancet 2015; Turtle et al. JCI 2016; Kochenderfer et al. JCO 2015; Turtle et al. JCI 2016; Gust et al. Cancer Disc. 2017

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Tools for Grading Neurotoxicity

Encephalopathy Assessment Tools for Grading of ICANS

CARTOX-10 [12]	ICE
• **Orientation:** orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points	• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points	• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point	• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point	• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
	• **Attention:** ability to count backwards from 100 by 10: 1 point

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.
Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

Lee DW, et al. (2018, December 19). ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation.* doi: https://doi.org/10.1016/j.bbmt.2018.12.758

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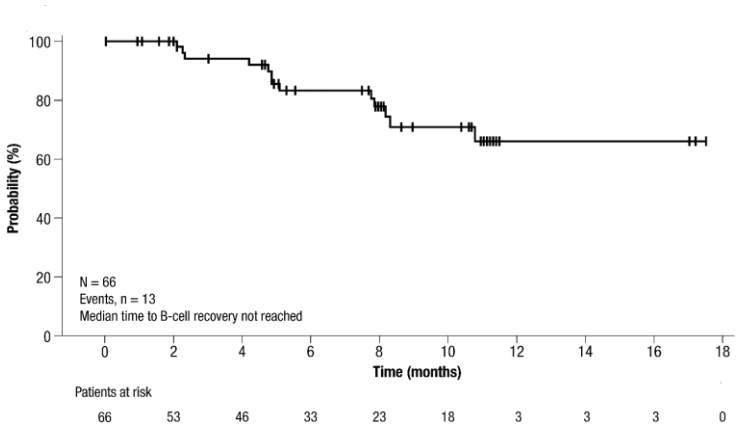
B-Cell Aplasia Following CAR-T



- All patients with a response to treatment had B-cell aplasia.
- The median time to B-cell recovery was not reached.
- The probability of maintenance of B-cell aplasia at 6 months after infusion was 83% (95% CI, 69 to 91).

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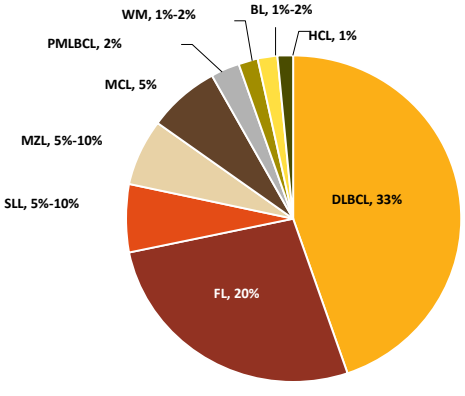
CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- **Diffuse Large B-Cell Lymphoma (DLBCL)**
- Mantle Cell Lymphoma (MCL)
- Follicular Lymphoma
- Marginal Zone Lymphoma

Relative Incidence of the Most Prevalent NHL Subtypes in the United States[1]



T-cell lymphomas constitute < 15% of all NHL cases.

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Treatment of Aggressive DLBCL

1. First Line: Chemotherapy (R-CHOP or R-EPOCH) + Anti-CD20 monoclonal antibody (Rituximab)
2. Common 2nd line regimens if disease comes back: R-ICE, R-DHAP, R-GemOx*

   ***These regimens may induce remission but response is generally short-lived due to lymphoma stem cells that are resistant to "standard doses" of chemotherapy**
3. Autologous stem cell transplant (ASCT)

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Autologous Stem Cell Transplant (ASCT)

- If a patient's lymphoma goes into remission with 2nd line treatment, ASCT is used to **maintain** the remission.
- During 2nd line treatment, a patient's healthy blood-producing cells are obtained and frozen.
- After completing 2nd line chemotherapy, patient receives a "high dose chemotherapy" regimen, followed by infusion of their own healthy blood-producing cells.

  -This helps prevent toxicity of the "high dose chemotherapy."

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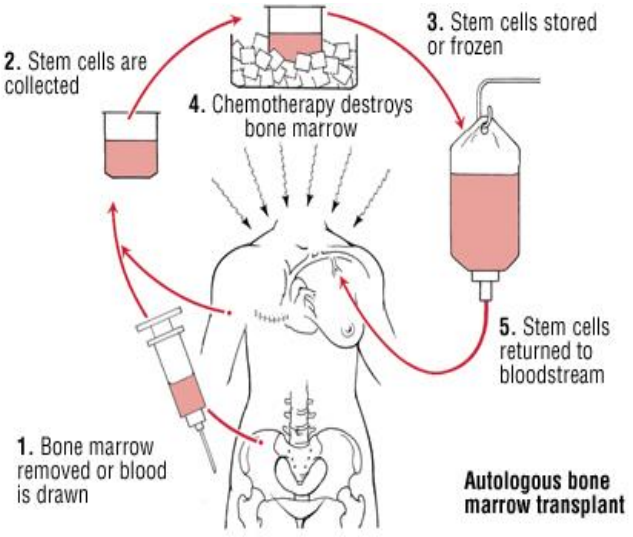
Autologous Stem Cell Transplant

- Must be in remission
- Stem cells derived from patient
- High dose chemotherapy
- Stem cell infusion
- Bone marrow recovers in 1.5-3 weeks
- Adverse effects in ~ 3-7%



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Treatment Challenges

- What if lymphoma comes back after an autologous stem cell transplant?
- What if lymphoma will not go into remission in order to proceed to an autologous stem cell transplant?

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Three Large Multicenter CAR T Studies for DLBCL

- Zuma-1 (Kite/Gilead) Axicabtagene Ciloleucel -> First FDA approval October 2017
  - Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (transformed follicular lymphoma, or tFL).
- Juliet (Novartis) Tisagenlecleucel -> FDA approval May 2018
  - Treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
- Transcend NHL 001 (Juno/Celgene) Lisocabtagene maraleucel

Neelapu SS, et al. N Engl J Med. Volume 377(26):2531-2544. December 28, 2017
Schuster et al. N Engl J Med. Volume 377(26):2545-2554. December 28, 2017
Abramson, Palomba et al. ICML 2017

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Three Major Anti-CD19 CAR T-cell Products for Lymphoid Malignancies

	Axicabtagene Ciloleucel- ZUMA-1	**Tisagenlecleucel JULIET**	**Lisocabtagene Maraleucel TRANSCEND NHL-001**
Construct	antiCD19-**CD28**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**41BB**-CD3z
T-cell Manufacturing	**Retroviral vector** Bulk T-cells	**Lentiviral Vector** Bulk T-cells	**Lentiviral Vector** CD4:CD8 1:1 ratio
Dose	2×10^6/kg (max 2×10^8)	0.6 to 6.0×10^8	DL1: 0.5×10^7, DL2: 1.0×10^8
Bridging Therapy	None allowed in pivotal trial but often used in standard practice	93%	72%
Lymphodepletion	Flu/Cy 500/30 x 3d	Flu/Cy 250/25 x 3d, or BR	Flu/Cy 300/30 x 3d
Treatment Locale	Inpatient Only	Inpatient and Outpatient*	Inpatient and Outpatient*
Approval Status	FDA approved for DLBCL, high-grade B-cell lymphoma, transformed FL, primary mediastinal B-cell lymphoma	FDA approved for pediatric ALL, DLBCL, high-grade B-cell lymphoma, transformed FL	Not yet FDA approved

* Outpatient therapy requires careful patient selection and is center dependent based on outpatient resources

1. Schuster SJ, et al. NEJM 2018; 2. Neelapu SS, et al. NEJM 2017; 3. Abramson JS, et al. ASCO 2019

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CART 19 Therapy Outcomes in R/R LBCL

	Zuma-1 (Axicabtagene Ciloleucel)	Juliet (Tisagenlecleucel)	Transcend NHL 001 (Lisocabtagene Maraleucel)
Pts leukapheresed, n	111, 108 infused	141, 111 infused	102, 70 infused
Histologies	Cohort 1: DLBCL Cohort 2: PMBCL, tFL	DLBCL/tFL	DLBCL, PMBCL, tFL, FL3b (CORE) TMZL, MCL, Richter's
Efficacy in R/R DLBCL Best OOR Best CRR 6 month CRR 12-mo PFS	 42% 40% 40%	 52% 40% 30% 83% in CR/PR pts at 3mo	 73% 53% 33% R/R DLBCL DL1, 46% DL2

1. Schuster SJ, et al. NEJM 2018; 2. Neelapu SS, et al. NEJM 2017; 3. Abramson JS, et al. ASCO 2019

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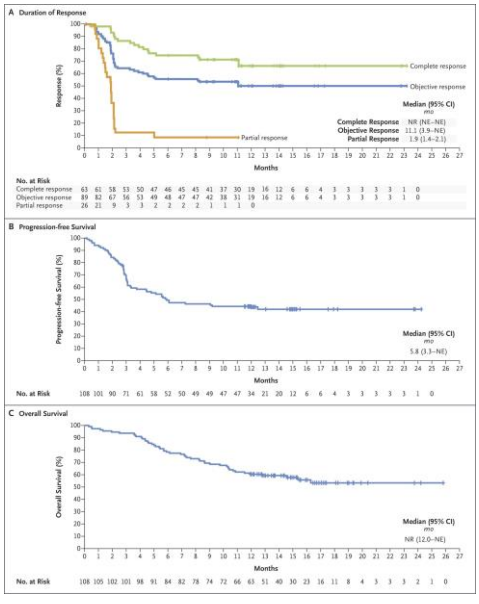
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory LBCL



Kaplan–Meier Estimates of the Duration of Response, Progression-free Survival, and Overall Survival.

Neelapu SS et al. N Engl J Med ;377:2531-2544

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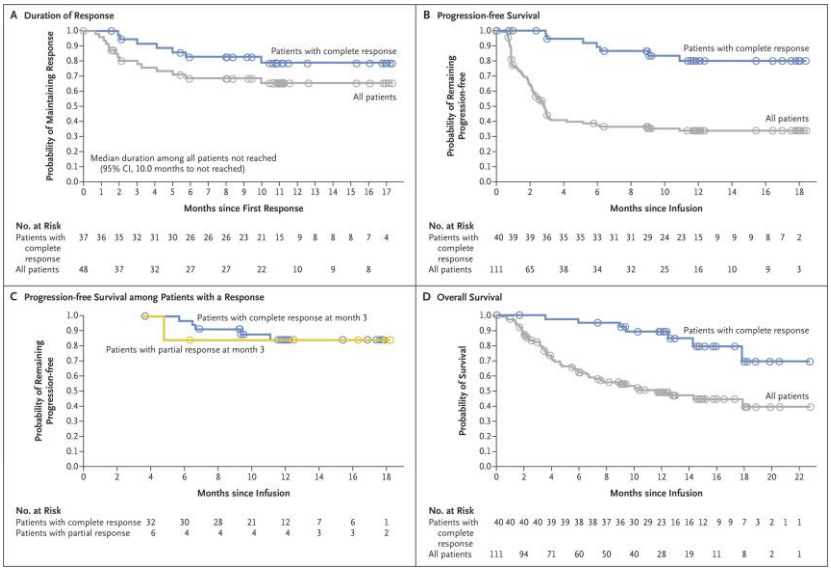
Tisagenlecleucel in Adult Relapsed or Refractory DLBCL

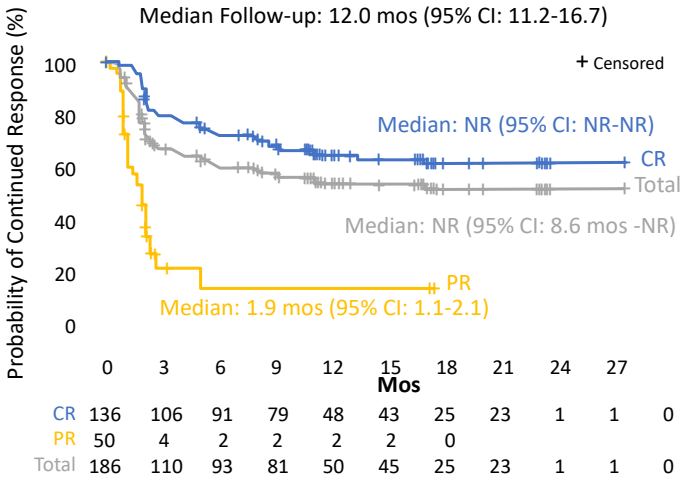


Duration of Response, Progression-free Survival, and Overall Survival

Schuster SJ et al. N Engl J Med 2019;380:45-56

Lisocabtagene Maraleucel in Adult R/R LBCL

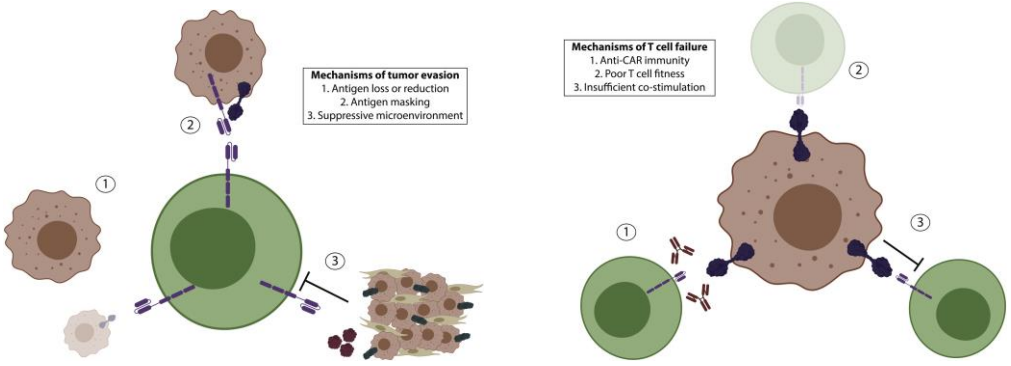
Efficacy-Evaluable Patients (N = 256)	
ORR (95% CI)	73 (67-78)
CR rate (95% CI)	53 (47-59)
Time to first CR or PR, median mos (range)	1.0 (0.7-8.9)
DoR at 6 mos, % (95% CI)	60.4 (52.6-67.3)
DoR at 12 mos, % (95% CI)	54.7 (46.7-62.0)



Abramson. ASH 2019. Abstr 241.

Why Doesn't CAR T-Cell Therapy Always Work?

- Leukemia relapse after CAR T-cells could be classified into 2 distinct types:
  - Loss of the CD19 target antigen on the surface of leukemia cells
  - Loss of CD19 CAR T-cells in blood (short persistence)



1. Grupp et al NEJM 2013; 2. Sotillo E, et al. *Cancer Discov*. 2015; 3. Jacoby E, et al. Nat Commun. 2016; 4. Turtle et al. JCI 2016
5. Nathan Singh N et al. Seminars in Cancer Biology, Volume 65,2020, Pages 91-98

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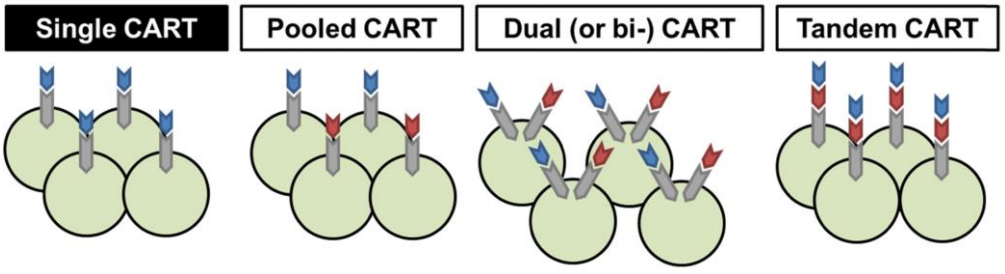
Strategies to Avoid Antigen-Loss Relapses

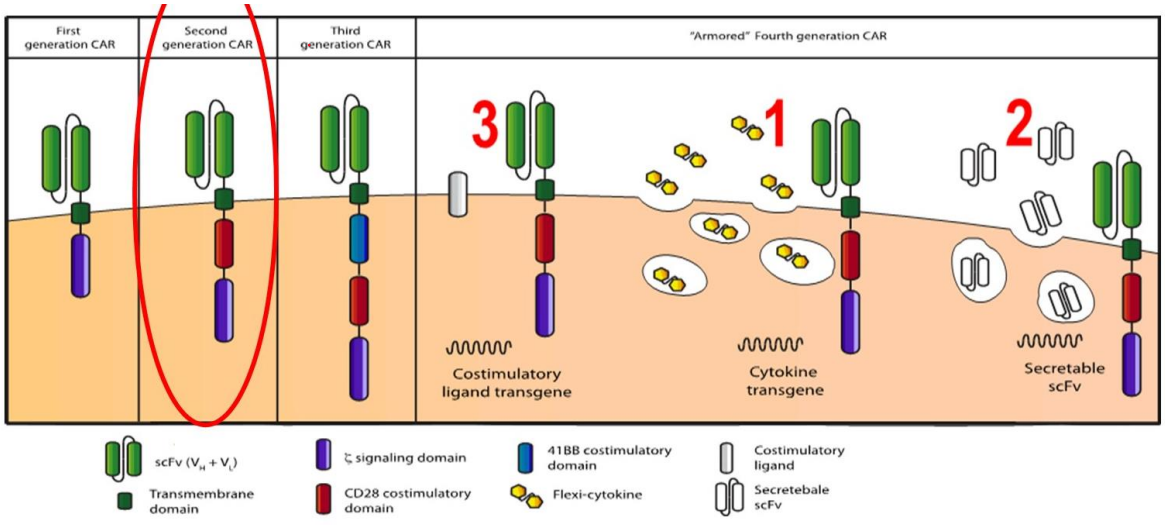


Single CART – CAR T cells of same specificity (i.e. CD19)
Pooled CART – 1:1 mixture of single–specificity CART: each cell remains able to recognize only one target (i.e. one with specificity for CD19, and one with specificity for CD22)
Dual (or bi-) CART – every T cell bears 2 distinct CAR structures able to recognize 2 different targets (i.e. one for CD19 and one for CD22)
Tandem CART – every T cell bears 1 CAR structure where 2 scFvs are built in series and are able to recognize 2 different targets

Marco Ruella, Marcela Maus. Computational and Structural Biotechnology Journal. 2016; (14):357-362

44

Evolution of CAR Design



Maria Lia Palomba ASCO 2019 Annual Meeting

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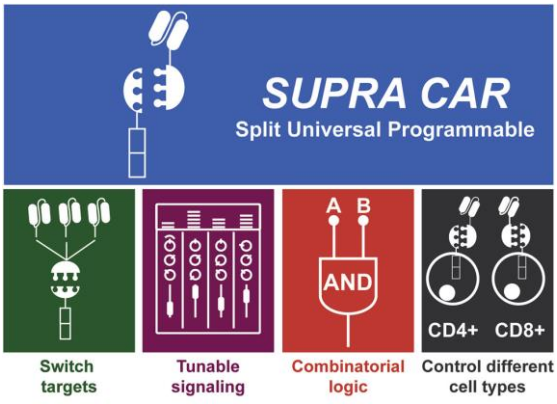

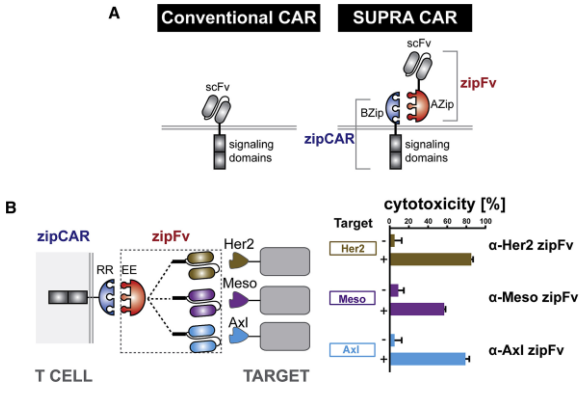

- Programmable system: universal receptor expressed on T cells and a tumor-targeting scFv adaptor molecule
- Targets multiple tumor antigens using different zipFvs
- SUPRA CARs can be finely regulated via multiple mechanisms to limit overactivation
- Variables manipulated: (1) the affinity between leucine zipper pairs, (2) the affinity between tumor antigen and scFv, (3) the concentration of zipFv, and (4) the expression level of zipCAR
- Effect on IFN-γ production by primary CD4+ T cells expressing RR zipCAR

Cho JH, et al. Cell 2018; 173 (6):1316-1317

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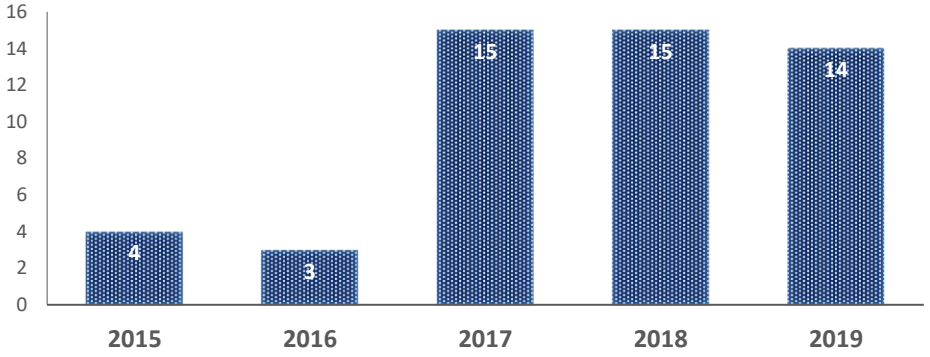
Why "humanize" CARs?

1. Immune rejection – loss of CAR cells (pedi- and adult B-ALL)
2. Superior efficacy? durability of response
3. Humanized CAR-T can rescue ~ 50% kids with B-ALL previously treated with murine CAR-T and relapsed (Shannon Maude, ASH 2017)



Number of trials utilizing humanized/fully human CAR constructs (binding domain/signaling domain. *Data source: CellTrials.org*

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Autologous CAR-T Cells vs Allogeneic CAR-T Cells

Patient Derived Limitations

- Cost
- Harvest and Manufacturing Failures
- Product Variability and Quality Control
- Disease Progression During Manufacture
- Contamination with Tumor cells
- Cancer Associated T-cell Dysfunction

Graham C, et al. *Cells* 2018, *7*, 155

Donor derived

- Previous HSCT donor
- Virus-specific CAR-T cells
- Gene-edited healthy donor CAR-T cells

Donor Derived Advantages

- Easier and cost-effective manufacturing
- Reduced time to CAR-T infusion
- Potential to treat all eligible patients on demand within days, no need for bridging
- Increase probability of healthy CAR-T cell generation
- Convenience of repeat dosing

Donor Derived Barriers

- Graft Versus Host Disease (gene editing techniques do not reach 100% knockout)
- Rejection of CAR-T Cells (less persistence)
- Off Target Cleavage with Gene Editing

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What's Else is Exciting in LBCL CAR-T?

Trial	Phase	Treatment	Population
TRANSFORM (NCT03575351)	III	Lisocabtagene maraleucel vs SoC	Transplant-eligible R/R aggressive B-cell NHL
BELINDA (NCT03568461)	III	Tisagenlecleucel vs SoC	R/R aggressive B-cell NHL
ZUMA-12 (NCT03761056)	II	Axicabtagene ciloleucel	High-risk large B-cell lymphoma; no prior treatment (1st line)
TRANSCEND-PILOT (NCT03483103)	II	Lisocabtagene maraleucel	R/R aggressive B-cell NHL after first-line immunochemotherapy, ineligible for ASCT
MB-CART2019.1 (NCT03870945)	I	Bispecific tandem CAR T construct against CD19 and CD20	R/R B-NHL without curative treatment option, or in 2nd line, non-transplant eligible DLBCL patients
ALEXANDER (NCT03287817)	I	AUTO3, the first CD19/22 dual targeting with pembrolizumab	R/R DLBCL
ALPHA (NCT03939026)		ALLO-501 and ALLO-647 anti CD19	R/R large B-cell or follicular lymphoma

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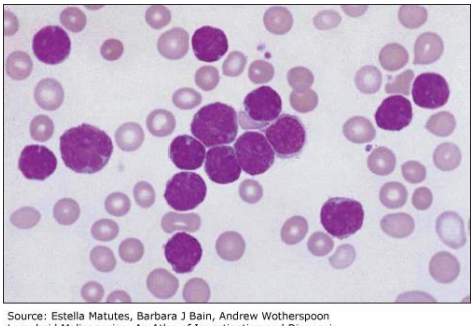
CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- Diffuse Large B-Cell Lymphoma (DLBCL)
- **Mantle Cell Lymphoma (MCL)**
- Follicular Lymphoma
- Marginal Zone Lymphoma



Source: Estella Matutes, Barbara J Bain, Andrew Wotherspoon
Lymphoid Malignancies: An Atlas of Investigation and Diagnosis
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Peripheral blood film in mantle cell lymphoma showing pleomorphic cells

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Phase II ZUMA-2 Trial of KTE-X19 CAR T-Cell Therapy in Relapsed/Refractory Mantle Cell Lymphoma (MCL)

- Mantle cell lymphoma is an uncommon, aggressive B-cell NHL subtype with hallmark chromosomal translocation t(11;14)(q13;q32)
- KTE-X19: autologous CD19-targeted CAR T-cell therapy comprising a CD3ζ T-cell activation domain and a costimulatory CD28 domain
- The phase II ZUMA-2 study sought to evaluate efficacy and safety of KTE-X19 in patients with relapsed/refractory MCL
- First CAR T-cell therapy, brexucabtagene autoleucel, FDA approved in 2020 for treatment of adults with R/R MCL

1. Martin. Blood. 2016;127:1559. 2. Jain. Br J Haematol. 2018;183:578. 3. Epperla. Hematol Oncol. 2017;35:528. 4. Sabatino. Blood. 2016;128:1227. 5. Wang. ASH 2019. Abstr 754.

ZUMA-2: Study Design

- Multicenter, global phase II trial

Patients with relapsed/refractory mantle cell lymphoma; 1-5 prior therapies; ≥ 1 measurable lesion; ECOG PS 0-1 (N = 74)

Optional Bridging Therapy
Dexamethasone 20-40 mg/d x 1-4 d, *or*
Ibrutinib 560 mg/d, *or*
Acalabrutinib 100 mg BID
(n = 25)

Conditioning Chemotherapy
Fludarabine 30 mg/m^2 +
Cyclophosphamide 500 mg/m^2
Days -5, -4, -3
(n = 69)

CAR T-Cells
KTE-X19
2 x 10^6 cells/kg, Day 0
(n = 68)

F/U begins with first tumor assessment on Day 28; BM biopsy may be required to confirm CR

Primary endpoint: ORR (IRRC-assessed per Lugano classification)

Secondary endpoints: DoR, PFS, OS, safety, ORR (investigator assessed), QoL (EQ-5D), CAR T-cell levels in blood and cytokines in serum

- KTE-X19 was successfully manufactured in 96% of patients and administered to 92% of patients
- Median time from leukapheresis to KTE-X19 delivery was 16 days

Wang. ASH 2019. Abstr 754.

Slide credit clinicaloptions.com

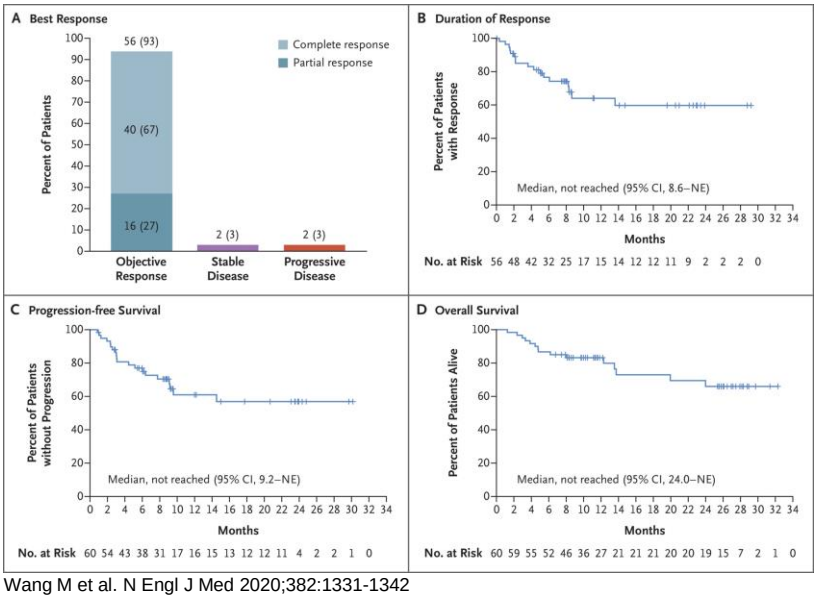
ZUMA-2: Baseline Characteristics

Characteristic	N = 68
Median age, yrs (range)	65 (38-79)
▪ ≥ 65 yrs, n (%)	39 (57)
Male, n (%)	57 (84)
Stage IV, n (%)	58 (85)
ECOG PS 0-1, n (%)	68 (100)
Int/high-risk MIPI, n (%)	38 (56)
Ki-67 index ≥ 50%, n/N (%)	34/49 (69)
TP53 mutation, n/N (%)	6/36 (17)
Bone marrow involvement, n (%)	37 (54)
Extranodal disease, n (%)	38 (56)
MCL morphology, n (%)	
▪ Classical	40 (59)
▪ Pleomorphic	4 (6)
▪ Blastoid	17 (25)

Wang. ASH 2019. Abstr 754.

53

ZUMA-2: Objective Response, Duration of Response, Progression-free Survival, and Overall Survival



- ORR of 93% (CR: 67%)
- Median DoR: not reached (95% CI: 8.6-NE)
  - 57% of all responders and 78% of those with a CR remained in remission
- Median f/u for initial 28 patients treated: 27 mos (range: 25.3-32.3)
  - 43% remained in remission without additional treatment
- ORR consistent across subgroups

Wang M et al. N Engl J Med 2020;382:1331-1342

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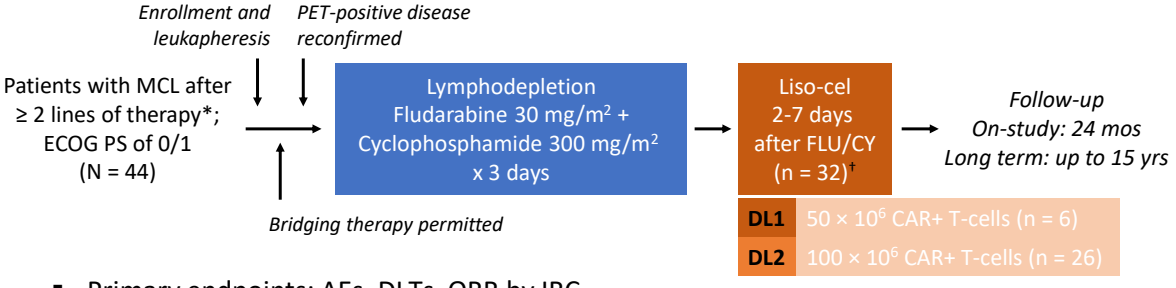
TRANSCEND NHL 001 (MCL Cohort): Study Design

- Multicenter, nonrandomized, open-label phase I study of Liso-cel, a CD19-directed CAR T-cell therapy with defined composition of CD8+ and CD4+ T-cell components administered separately at equal target doses



- Primary endpoints: AEs, DLTs, ORR by IRC
- Secondary endpoints: CR rate by IRC, DoR, PFS, OS, cellular kinetics, HRQoL, no. ICU days

*Prior BTK inhibitor, alkylating agent, and anti-CD20 agent. Original protocol did not require prior treatment, allowed enrollment of R/R patients with ≥ 1 line of prior MCL therapy and ECOG PS of 2. Prior autologous or allogeneic HSCT allowed. †1 additional patient received nonconforming product where either CD8 or CD4 cell component did not meet requirement to be considered liso-cel.

Palomba. ASH 2020. Abstr 118. NCT02631044.

Slide credit clinicaloptions.com

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TRANSCEND NHL 001 (MCL Cohort): Baseline Characteristics

Characteristic	Liso-cel (N = 32)
BM involvement at infusion,* n (%)	8 (25)
Median prior therapies, n (range) ▪ ≥ 3 prior therapies, n (%)	3 (1-7) 22 (69)
Prior HSCT, n (%) ▪ Allogeneic/autologous	11 (34) 3 (9)/10 (31)
Refractory, n (%)	26 (81)
Prior BTK inhibitor, n (%) ▪ Prior ibrutinib ▪ Refractory to prior ibrutinib‡	28 (88) 24 (75) 10 (31)
Prior venetoclax, n (%) ▪ Refractory to prior venetoclax	8 (25) 5 (16)
Bridging therapy, n (%) ▪ Systemic treatment only ▪ Radiotherapy only ▪ Systemic therapy and radiotherapy	17 (53) 12 (37.5) 1 (3) 4 (12.5)

Characteristic	Liso-cel (N = 32)
Median age, yrs (range) ▪ ≥ 65 yrs of age, n (%)	67 (36-80) 21 (66)
Male, n (%)	27 (84)
ECOG PS 0/1 at screening, n (%)	16 (50)/16 (50)
Blastoid morphology, n (%)	13 (41)
Ki67 ≥ 30%, n (%)	23 (72)
TP53 mutations, n (%)	7 (22)
SPD ≥ 50 cm² prior to LDC,§ n (%)	5 (17)
LDH > ULN prior to LDC, n (%)	16 (50)
CRP ≥ 20 mg/L at baseline,‖ n (%)	17 (55)
Secondary CNS lymphoma at time of liso-cel administration, n (%)	1 (3)

Best response of PR, SD, or PD to last systemic or transplant treatment with curative intent.
Best response of PD.

Palomba. ASH 2020. Abstr 118.

Slide credit: clinicaloptions.com

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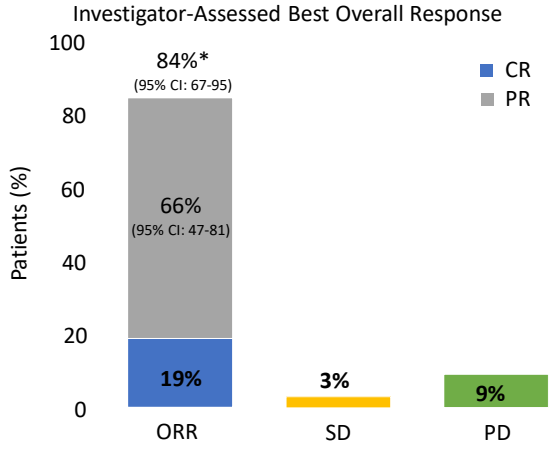
TRANSCEND NHL 001 (MCL Cohort): Response



Response by Subgroup, %	ORR	CR
Ki67 ≥ 30% (n = 23)	83	65
Blastoid morphology (n = 13)	77	54
TP53 mutations (n = 7)	100	57

- Median on-study follow-up: 5.9 mos (range: 0.4-24.8)
- Median time to first CR or PR: 0.95 mos (range: 0.9-2.0)

*Based on n = 32 treated; n = 1 not evaluable, not shown.

Palomba. ASH 2020. Abstr 118. Reproduced with permission.

Slide credit clinicaloptions.com

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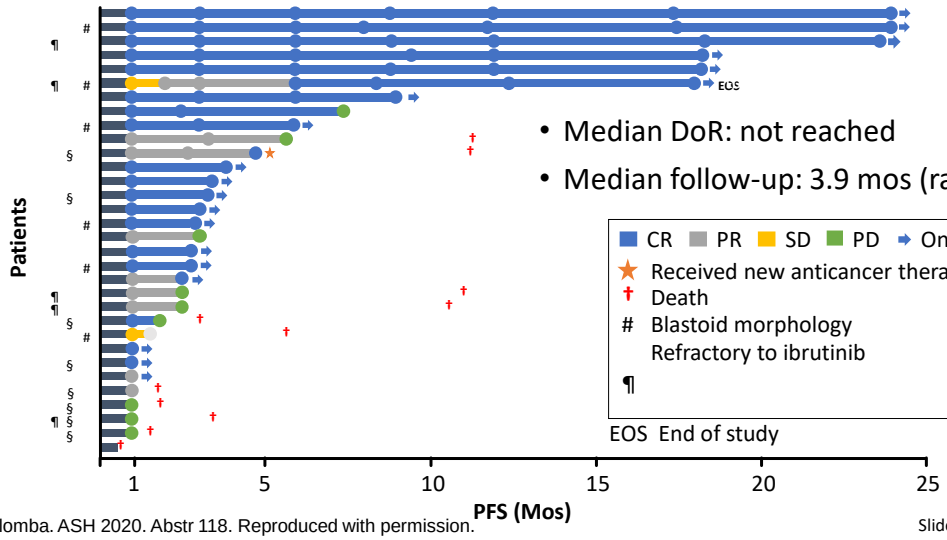
TRANSCEND NHL 001 (MCL Cohort): Response Over Time



- Median DoR: not reached
- Median follow-up: 3.9 mos (range: 0-21.3)

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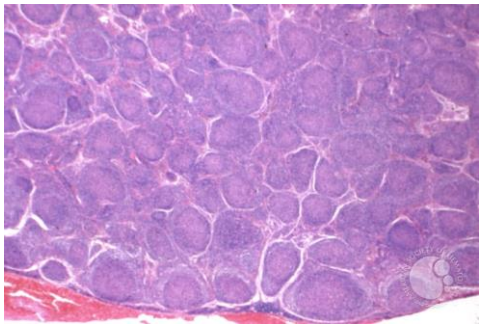
CAR T-Cell Therapy in B-Cell Non-Hodgkin Lymphoma (NHL)

- Diffuse Large B-Cell Lymphoma (DLBCL)
- Mantle Cell Lymphoma (MCL)
- **Follicular Lymphoma**
- **Marginal Zone Lymphoma**



ASH Image Bank – American Society of Hematology

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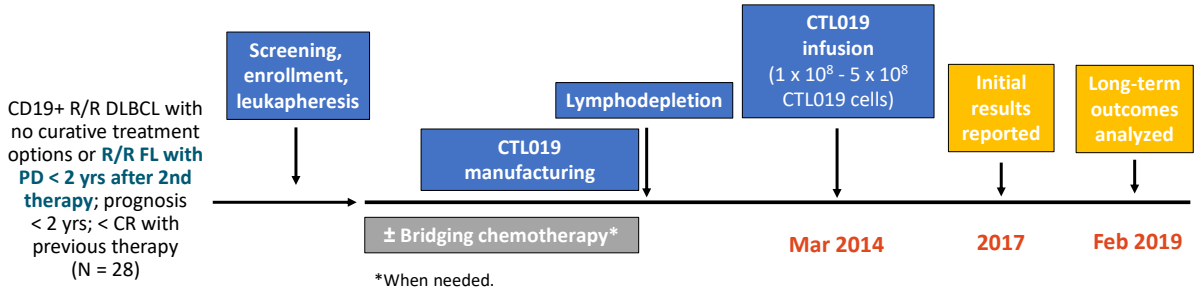
UPenn CAR-T-cells (CTL019) in R/R CD19+ B-Cell NHLs

- Single-center trial at University of Pennsylvania; CTL019 construct: α-CD19-4-1BB-CD3ζ



- Primary endpoint: ORR at 3 mos
- Secondary endpoints: PFS, RD, OS

Schuster. NEJM. 2017;377:2545. NCT02030834

Slide credit: clinicaloptions.com

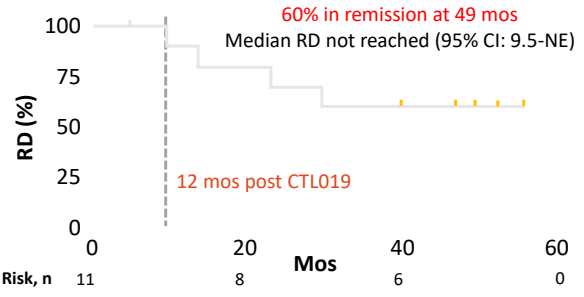
60

UPenn CTL019 in Follicular Lymphoma: 4-Yr Follow-up

Characteristic	FL
Enrolled, N	16
Infused, n	14
Median age, yrs (range)	59 (43-72)
Female, n (%)	9 (64)
Prior Rx, median n (range)	5 (2-10)
Advanced stage, n (%)	14 (88)
ECOG PS, median (range)	0 (0-1)
Prior HCT, n (%)	4 (25)
Bridging therapy, n (%)	10 (71)

Best ORR: 78%; CR, 71% (10/14); PR, 7% (1/14)
Median PFS: 32 mos (95% CI: 3.5-NE);
60% progression free at 49 mos
OS: 64% alive at 49 mos

Response Duration



Chong. ICML 2019. Abstr 090.

Slide credit: clinicaloptions.com

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ZUMA-5: Phase II Trial of Axicabtagene Ciloleucel (Axi-Cel) in High-Risk R/R Indolent NHL

Patients with high risk* indolent FL or MZL after ≥ 2 prior lines of CIT; ECOG PS 0/1; no CNS involvement or transformed disease (planned N = 160; n = 96 for efficacy analysis†)

Lymphodepleting Conditioning Regimen

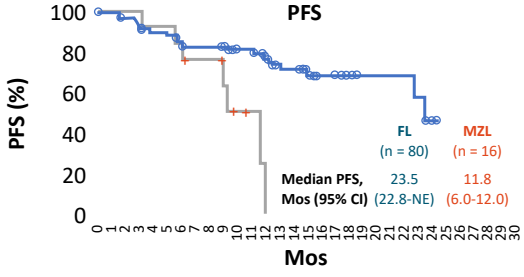
Leukapheresis

Cyclophosphamide + Fludarabine on Days -5 to -3

Axicabtagene Ciloleucel† IV on Day 0

Patients followed up to 15 yrs for safety

*High risk: with POD24, relapse post ASCT, or PD within 6 mos of second-line CIT or beyond.
†**n = 80 with FL and ≥ 9 mos of f/u; n = 16 with MZL and ≥ 1 mo of f/u.** Axi-cel: CD19-directed CAR T-cell therapy.



- Manageable toxicity profile with axi-cel; early onset of adverse events, generally reversible

Jacobson. ASCO 2020. Abstr 8008. NCT03105336.

Slide credit: clinicaloptions.com

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ZUMA-5: Axicabtagene Ciloleucel in iNHL

Characteristic	FL n = 80	MZL n = 16	All Patients N = 96
Median age (range), years	62 (34 – 79)	67 (52 – 77)	63 (34 – 79)
≥ 65 years, n (%)	29 (36)	11 (69)	40 (42)
Male, n (%)	43 (54)	4 (25)	47 (49)
ECOG PS 1, n (%)	33 (41)	6 (38)	39 (41)
Stage IV disease, n (%)	37 (46)	13 (81)	50 (52)
≥ 3 FLIPI, n (%)	38 (48)	11 (69)	49 (51)
High tumor bulk (GELF criteria), n (%)[a]	40 (50)	7 (44)	47 (49)
Median no. of prior therapies (range)	3 (2 – 9)	3 (2 – 8)	3 (2 – 9)
≥ 3, n (%)	56 (70)	11 (69)	67 (70)
Prior PI3Ki therapy, n (%)	26 (33)	6 (38)	32 (33)
Refractory disease, n (%)[b]	59 (74)	11 (69)	70 (73)
POD24 from first anti-CD20 mAb-containing therapy, n (%)[c]	45 (56)	7 (44)	52 (54)
Prior autologous SCT, n (%)	19 (24)	3 (19)	22 (23)

Jacobson. ASCO 2020. Abstr 8008. NCT03105336.

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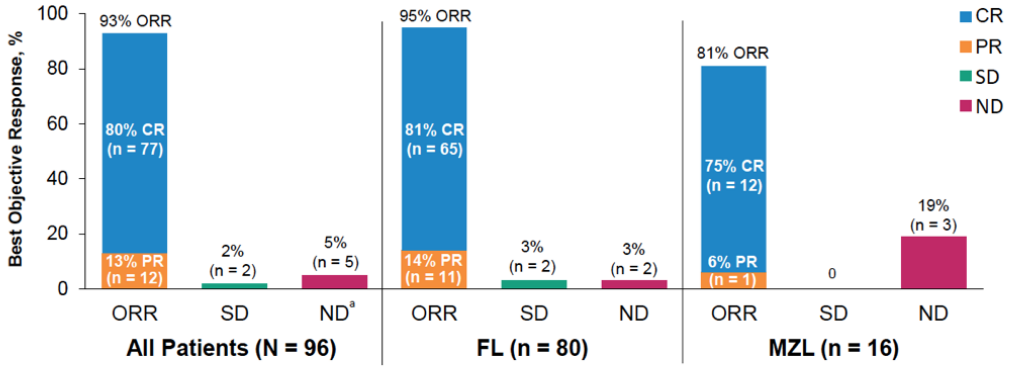
ZUMA-5: Axicabtagene Ciloleucel in iNHL



- The median time to first response was 1 month (range, 0.8 – 3.1)
- Of the 80 patients with FL, 10 (13%) had an initial response of PR at Week 4 and later converted to CR

Jacobson. ASCO 2020. Abstr 8008. NCT03105336.

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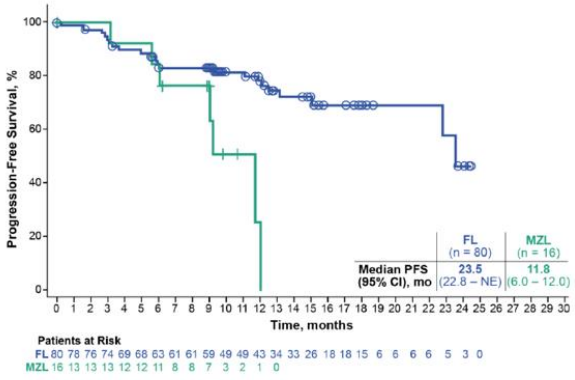
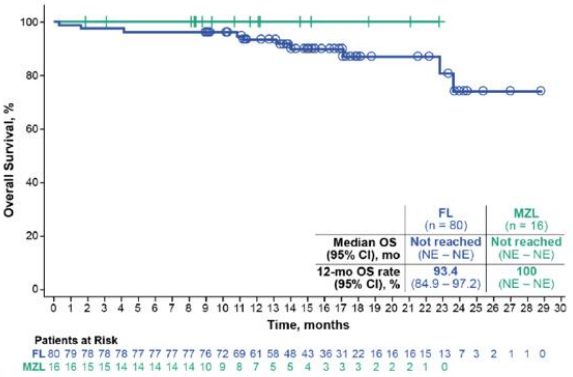
ZUMA-5: PFS and OS with Axicabtagene Ciloleucel in iNHL





- With a median follow-up of 15.3 months, median PFS was 23.5 months (95% CI, 22.8 – NE) in all patients, and the median OS was not reached
  - The 12-month OS rate was 94.3% (95% CI, 86.8 – 97.6) for all patients

Jacobson. ASCO 2020. Abstr 8008. NCT03105336.

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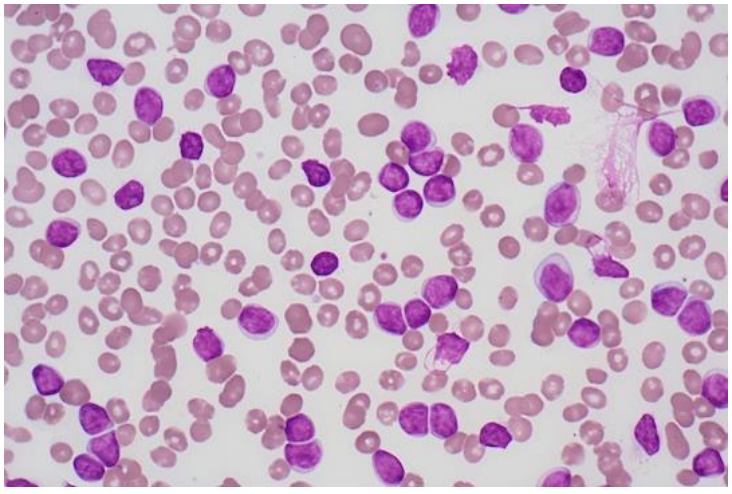
CAR T-Cell Therapy in Chronic Lymphocytic Leukemia (CLL)



Increased numbers of mature lymphocytes in peripheral blood

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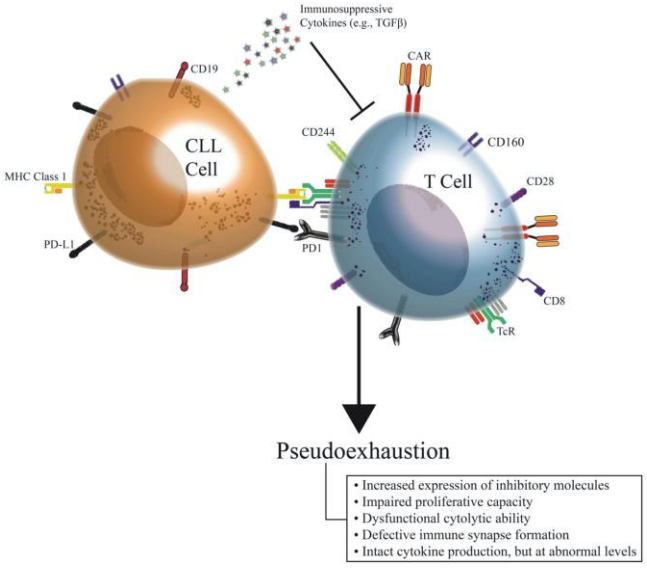
Improving CLL Therapy with CAR T-cells



Fraietta JA, Schwab RD, Maus MV. Semin Oncol. 2016 Apr;43(2):291-9.

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Feasibility and efficacy of JCAR014 CD19-targeted CAR T cells with concurrent ibrutinib* for CLL after ibrutinib failure

Patient Characteristics (n=36)	Ibr Cohort (n=17)	No-Ibr Cohort (n=19)	P value
Number of prior therapies	5 (4,7)	5 (4,6)	0.55
Prior progression on Ibrutinib	16 (94%)	18 (95%)	1.00
CRS			
None	4 (24%)	2 (11%)	0.39
Any grade	13 (76%)	17 (89%)	0.39
CRS grade 0-2	17 (100%)	14 (74%)	0.05
CRS grade 3-5	0 (0%)	5 (26%)	0.05
Neurotoxicity			
None	12 (71%)	11 (58%)	0.50
Any Grade	5 (29%)	8 (42%)	0.50
OR at 4 wks 2008 iwCLL	14 (88%)	10 (56%)	0.06
Nodal response at 4 wks CR/PR	10 (83%)	10 (59%)	0.23

* Ibrutinib was scheduled to begin ≥2 weeks before leukapheresis and continue for ≥3 months after CAR T-cell infusion.

Gauthier et al., Blood, 2018

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CAR-T and Ibrutinib in CLL: Sequential or simultaneous?

- CD19 CAR T-cell therapy with concurrent ibrutinib is well tolerated.
- The 4-week ORR using 2018 International Workshop on CLL (iwCLL) criteria is higher with Ibrutinib combination, and more patients achieve a minimal residual disease (MRD)-negative marrow response by *IGH* sequencing.
- The 1-year overall survival and progression-free survival (PFS) probabilities are higher higher with Ibrutinib combination.
- Compared with CLL patients treated with CAR T cells without ibrutinib, CAR T cells with concurrent ibrutinib were associated with lower CRS severity and lower serum concentrations of CRS-associated cytokines, despite equivalent in vivo CAR T-cell expansion.

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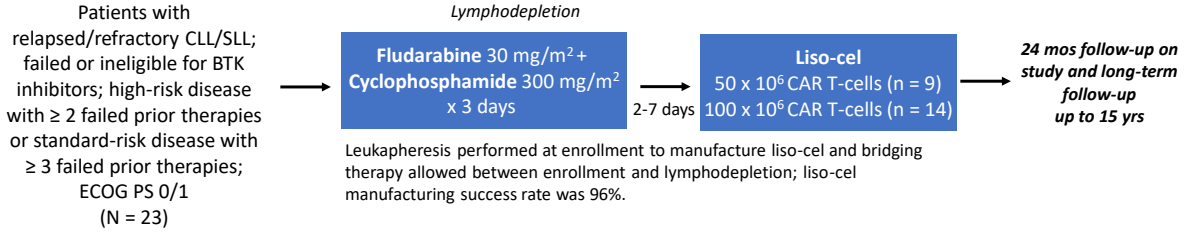
TRANSCEND JCAR017 CLL 004: Study Design

- Multicenter, open-label phase I/II study



- Primary endpoints: safety and RP2D
- Exploratory endpoints: antitumor activity and pharmacokinetic profile

Siddiqi. ASH 2019. Abstr 503. NCT03331198.

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TRANSCEND JCAR17 CLL 004: Baseline Characteristics

Characteristic	Total Patients (N = 23)
Any high-risk features, n (%) ▪ del(17p) ▪ *TP53* mutation ▪ Complex karyotype*	19 (83) 8 (35) 14 (61) 11 (48)
Median number of prior therapies (range)	5 (2-11)
Prior ibrutinib, n (%)	23 (100)
Ibrutinib refractory/relapsed, n (%)	21 (91)
BTK inhibitor progression and failed venetoclax,† n (%)	9 (39)

*≥ 3 chromosomal abnormalities. †Discontinuation due to PD or less than PR after ≥ 3 mos of therapy.

Siddiqi. ASH 2019. Abstr 503.

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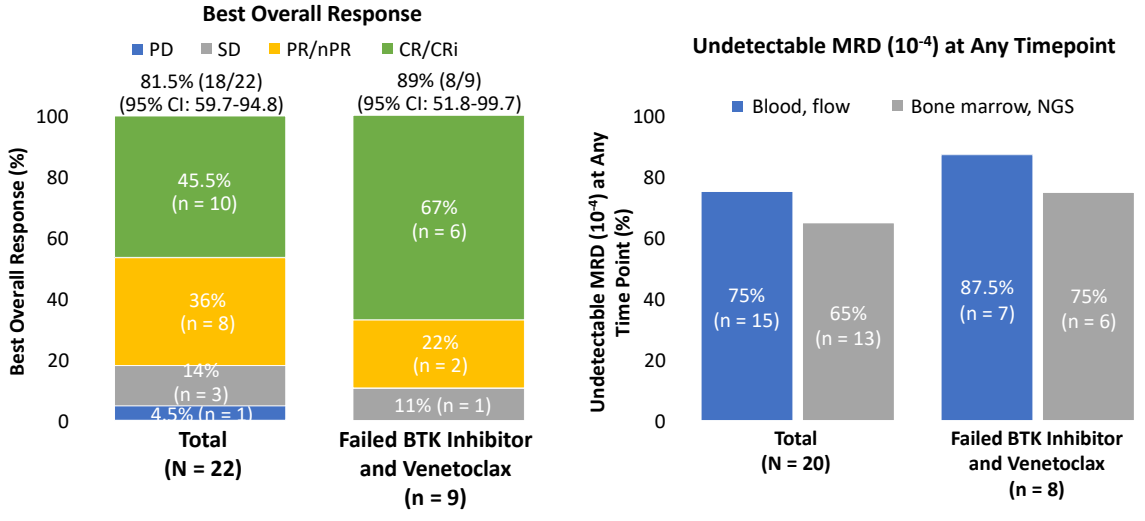
TRANSCEND JCAR17 CLL 004: Responses and MRD



Median follow-up: 11 mos

Siddiqi. ASH 2019. Abstr 503. Reproduced with permission.

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TRANSCEND JCAR17 CLL 004 Ibrutinib Combination Cohort

Patients with R/R CLL/SLL who:
- Progressed on ibrutinib *OR*
- Had high-risk features† and received ibrutinib for ≥ 6 mos with < CR *OR*
- Had *BTK* or *PLCg2* mutations *OR*
- Had prior ibrutinib and no contraindication to restarting ibrutinib

(N = 19)

- Analysis of phase I combination cohort of multicenter, open-label, multicohort phase I/II study

Lymphodepletion	Dose Escalation	Dose Expansion	
Fludarabine 30 mg/m^2 + **Cyclophosphamide** 300 mg/m^2 x 3 days	**Liso-cel* DL1 or DL2 +** Ibrutinib 420 mg	**Liso-cel DL2 +** Ibrutinib 420 mg	***24 mos follow-up on study and long-term follow-up up to 15 yrs***

Leukapheresis performed at enrollment to manufacture liso-cel and bridging therapy allowed between enrollment and lymphodepletion; liso-cel manufacturing success rate was 100%.
*DL1: 50 x 10^6 CAR T-cells; DL2: 100 x 10^6 CAR T-cells. †Complex cytogenetic abnormalities, del (17p), *TP53* mutated, or unmutated *IGHV*.

- Primary endpoints: safety and recommended dose determination
- Exploratory endpoints: antitumor activity and cellular kinetic profile

Wierda. ASH 2020. Abstr 544. NCT03331198.

Slide credit: clinicaloptions.com

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TRANSCEND CLL 004 Combination Cohort: Baseline Characteristics

Characteristic	Total Patients (n = 19)	Liso-cel DL1 + Ibrutinib (n = 4)	Liso-cel DL2 + Ibrutinib (n = 15)
Any high-risk features, n (%) ▪ del(17p) ▪ *TP53* mutation ▪ Complex karyotype*	18 (95) 8 (42) 6 (32) 8 (42)	4 (100) 2 (50) 1 (25) 3 (75)	14 (93) 6 (40) 5 (33) 5 (33)
Median no. prior therapies (range)	4 (1-10)	4.5 (1-5)	3 (2-10)
▪ Prior ibrutinib, n (%)	19 (100)	4 (100)	15 (100)
▪ Ibrutinib relapsed/refractory, n (%)	19 (100)	4 (100)	15 (100)
▪ Prior BTKi and venetoclax, n (%)	11 (58)	2 (50)	9 (60)

≥ 3 chromosomal abnormalities.

Wierda. ASH 2020. Abstr 544.

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TRANSCEND CLL 004 Combination Cohort: Efficacy

Efficacy Outcome	Total Patients (n = 19)	Liso-cel DL1 + Ibrutinib (n = 4)	Liso-cel DL2 + Ibrutinib (n = 15)
ORR, n (%)	18 (95)	3 (75)	15 (100)
▪ CR/CRi	12 (63)	2 (50)	10 (67)
▪ PR	6 (32)	1 (25)	5 (33)
Undetectable MRD ≤ 10^{-4}, n (%)			
▪ PB by flow cytometry	17 (89)	3 (75)	14 (93)
▪ BM by NGS	15 (79)	3 (75)	12 (80)

- Median follow-up: 10 mos
- All 18 responders achieved a response by day 30 after liso-cel; all 17 patients who achieved undetectable MRD in PB did so by Day 30
- Among 18 patients with ≥ 6 mos of follow-up, 16 maintained or improved response from Day 30

Wierda. ASH 2020. Abstr 544.

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TRANSCEND CLL 004 Combination Cohort: Conclusions

- Liso-cel plus ibrutinib was generally well tolerated in heavily pretreated patients with R/R CLL/SLL in preliminary analysis of the phase I TRANSCEND CLL 004 trial, with low rates of grade 3 CRS/NEs and no grade 4/5 events
- Liso-cel plus ibrutinib treatment associated with rapid responses, high ORRs, and high rates of patients achieving undetectable MRD
  - ORR: 95% in overall patient population
  - Undetectable MRD in overall patient population: 89% in blood, 79% in bone marrow
- Study ongoing and actively enrolling patients

Wierda. ASH 2020. Abstr 544.

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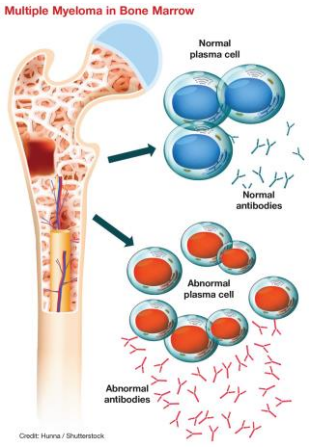
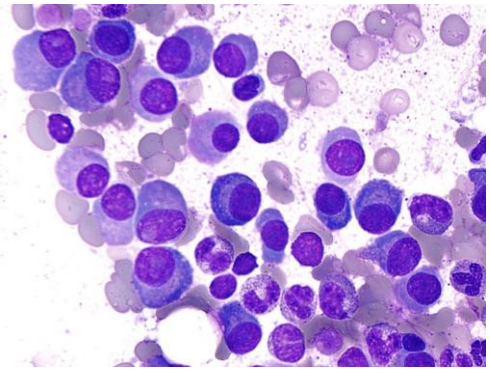
CAR T- Cell Therapy in Multiple Myeloma (MM)





Clinician Reviews. 2018 January;28(1):16-18,20-21

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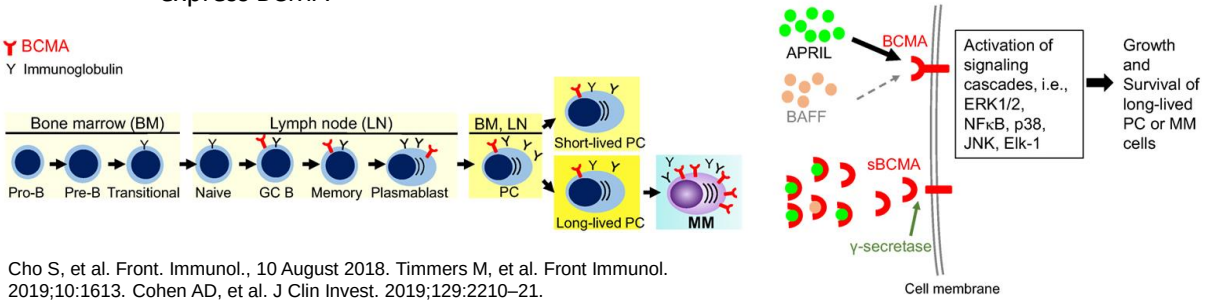
B-cell Maturation Antigen (BCMA)

- Functions to maintain long-lived plasma cell homeostasis
  - Essential in regulating B-cell maturation and differentiation
- Highly expressed on malignant plasma cells in MM
  - Increased expression associated with progression of disease
- BCMA shed from the surface of plasma cells leads to soluble BCMA (sBCMA) detectable in circulation
- Higher concentrations of sBCMA associated with poorer outcomes
  - Low level expression on healthy differentiated B-cells; no other normal cells/tissues express BCMA



Cho S, et al. Front. Immunol., 10 August 2018. Timmers M, et al. Front Immunol. 2019;10:1613. Cohen AD, et al. J Clin Invest. 2019;129:2210–21.

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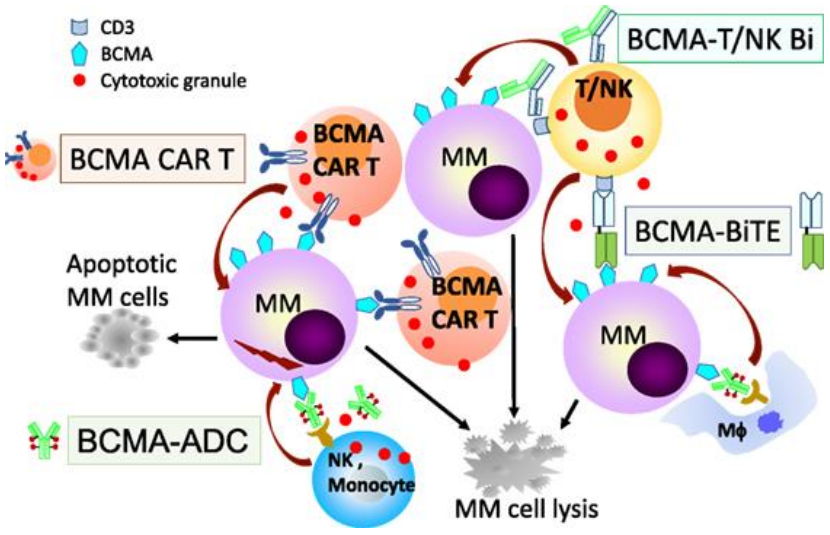
B-Cell Maturation Antigen (BCMA)-Based Immunotherapies



Cho S., Anderson KC., Tai Y. Front. Immunol., 10 August 2018.

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Phase I NCI BCMA CAR

- Single-center, open-label phase I trial in patients with R/R MM, N=16
- CD28 costimulatory domain, gamma-retroviral vector, dose levels: 0.3, 1, 3, and 9 ×106 CAR T-cells/kg
- Lymphodepletion: Flu 30 mg/m2 and Cy 300 mg/m2 daily on days −5 to −3

Baseline Characteristics		**Results**		**Adverse Events and Management**	
Median lines of prior therapy	9.5	PR or better	13 (81%)	Grade 3-4 CRS	6 (37.5%)
High risk cytogenetics	40%	Median EFS	31 weeks	Tocilizumab	5 (31%)
Del(17p)	33%	DoR >1 year	5 (31%)	Tocilizumab + steroids	4 (25%)
Refractory to last treatment	63%	DoR > 6 months	9 (56%)		

Brudno JN, et al. J Clin Oncol. 2018;36:2267–80.

80

Phase I Data: BCMA-Directed CAR T Cells in Multiple Myeloma

	BB2121 (BLUEBIRD) Idecabtagene vicleucel	LCAR-B38M (LEGEND)	JCARH125 (JUNO)
Population	33	57	44
# Prior Tx	7	3	7
CART Dose	50-800 x 106	0.07-2.1 x 106/kg	50-450 x 106
ORR	85%	88%	82%
CR	45%	74%	27%
CRS All Grades (Grade 3/4)	76% (6%)	89% (7%)	80% (9%)
Med Onset of CRS	2d	9d	3d
Neurotox All Grades (Grade 3/4)	42% (3%)	2% (0%)	25% (7%)
Med PFS	11.8 months	15 months	-

Raje et al, NEJM 2019; Zhao et al, ASH 2018, Mailankody et al, ASH 2018.

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Pivotal Phase II KarMMa trial of Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T-cell therapy, in R/R MM

Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Total (N=128)
ORR, n (%)	2 (50)	48 (69)	44 (82)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	19 (35)	40 (31)
Median DoR*, mo	†	9.9	11.3	10.6
Median PFS*, mo	†	5.8	11.3	8.6
CRS overall / Gr ≥3, n (%)	2 (50) / 0	53 (76) / 4 (6)	52 (96) / 3 (6)	107 (84) / 7 (5)
Median onset / duration, d	7 / 5	2 / 4	1 / 7	1 / 5
NT overall / Gr ≥3, n (%)	0 / 0	12 (17) / 1 (1)	11 (20) / 3 (6)	23 (18) / 4 (3)
Median onset / duration, d	NA	3 / 3	2 / 5	2 / 3

Munshi NC ASCO20 Abstr 8503

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Phase 1/2 CARTITUDE-1 (UPDATED)

- Open-label phase 1/2 trial of JNJ-4528 in R/R MM, N=29
- Pts received ≥3 prior regimens or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and received an anti-CD38 antibody.
- Lymphodepletion: Flu 30 mg/m2 and Cy 300 mg/m2 daily x 3 days
- As of 17 Jan 2020, median follow-up is 9 mo (3–17)

Baseline Characteristics		**Results**		**Adverse Events and Management**	
Median lines of prior therapy	5 (3-18)	ORR	100%	CRS	27 (93%)
Triple refractory to a PI, IMiD, and anti-CD38 antibody	86%	sCR	22 (76%)	Grade 1-2 Grade 3 CRS/Grade 5 CRS	n=25 n=1, n=1
Penta-refractory to 2 IMiDs, 2 PIs, and Daratumumab	31%	VGPR	6 (21%)	Grade 1 NT/Grade 3 NT	n=3, n=1
		PR	1 (3%)		

Berdeja JG et al. JCO 2020 38:15_suppl, 8505-8505

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Phase 1/2 CARTITUDE-1 (UPDATED)

- Median time to ≥CR was 2 months (range 1–9).
- 26/29 pts are progression-free, with 6-mo progression-free survival rate of 93% and longest response ongoing at 15 mo.
- All 16 pts (14 sCR, 2 VGPR) evaluable at 6 months were minimal residual disease negative at 10^{-5} or 10^{-6}.
- At 6-mo individual follow-up, 22/28 pts had JNJ-4528 CAR+ T cells below the level of quantification (2 cells/μL) in peripheral blood, suggesting CAR-T persistence in peripheral blood did not seem to correlate with deepening of response.
- **Conclusions:** JNJ-4528 treatment led to responses in all pts. These responses were early, deep, and durable at a low dose of CAR-T cells with 26/29 (90%) pts progression free at median 9-mo follow-up. CRS was manageable in most pts, supporting outpatient dosing.

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Universal: An Allogeneic First-in-Human Study of the Anti-BCMA ALLO-715 and the Anti-CD52 ALLO-647 in Relapsed/Refractory Multiple Myeloma

- Autologous anti-BCMA CAR T-cell therapy proven efficacious
  - Access limited by logistics, wait time, and bridging treatment
- Allogeneic anti-BCMA CAR T-cell or "off-the-shelf" therapy options avoids some challenges
  - Simplified, scalable manufacturing process with less product variability
  - Patients can be treated within days, resulting in less treatment delays or need for bridging therapy, with option for convenient repeat dosing
- Phase I UNIVERSAL study is the first in-human trial of allogeneic anti-BCMA CAR T-cell therapy; enrolled heavily pretreated patients with R/R MM

1. Cho. Cancers (Basel). 2020;12: 1473. 2. Mailankody. ASH 2020. Abstr 129.

Slide credit: clinicaloptions.com

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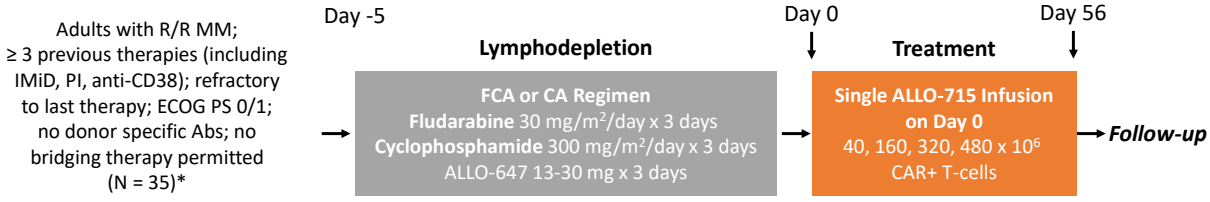
First-in-Human Phase I Trial (UNIVERSAL): Study Design

- Multicenter, open-label, dose-escalation phase I study



- Primary endpoint: safety and tolerability
- Secondary endpoints: lymphodepletion regimen and recommended ALLO-715 phase II dose; anti-tumor activity (ORR, DoR, PFS, MRD); ALLO-715 cellular kinetics; ALLO-647 PK data

*4 patients ineligible due to organ failure from PD; 31 patients evaluated in safety analysis; 26 patients reached assessment point and included in efficacy analysis.

Mailankody. ASH 2020. Abstr 129.

Slide credit clinicaloptions.com

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First-in-Human Phase I Trial (UNIVERSAL): Baseline Characteristics

- Median time from enrollment to start of treatment: 5 days

CAR T-Cell Dose	Lymphodepletion Regimen, n		
	FCA + Low-Dose ALLO-647	FCA + High-Dose ALLO-647	CA + Low-Dose ALLO-647
40 x 10^6 cells	3	--	--
160 x 10^6 cells	4	--	3
320 x 10^6 cells	6	4	3
480 x 10^6 cells	3	--	--

- Median follow-up: 3.2 mos

Characteristic, %	Safety Population (N = 31)
Median age, yrs (range)	65 (46-76)
Male	61
ECOG PS 0/1	48/52
ISS stage ≥ 2	74
High-risk cytogenetics*	48
Extramedullary disease	23
High tumor burden (> 50% BMPCs)	39
Median time since diagnosis, yrs (range)	5.4 (0.9-20.1)
Median prior tx regimens, n (range)	5 (3-11)
Prior ASCT	94
Penta exposed	94

Mailankody. ASH 2020. Abstr 129.

Slide credit: clinicaloptions.com

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First-in-Human Phase I Trial (UNIVERSAL): Response Rate

- 60% of patients in FCA plus 320 x 10^6 dose of ALLO-715 cohort responded to treatment; 40% achieved ≥ VGPR[1]
- 5/6 patients assessed with ≥ VGPR had negative MRD status[1]

Cell Dose and LD Regimen	FCA Cohort						CA Cohort	
ALLO-715	40	160	320	320	320	480	160	320
ALLO-647	Low (n = 3)	Low (n = 4)	Low (n = 6)	High (n = 4)	All (n = 10)	Low (n = 3)	Low (n = 3)	Low (n = 3)
ORR, n (%)	--	2 (50)	3 (50)	3 (75)	6 (60)	1 (33)	--	2 (67)
≥ VGPR, n (%)	--	1 (25)	3 (50)	1 (25)	4 (40)	--	--	1 (33)

1. Mailankody. ASH 2020. Abstr 129. 2. Kumar. Lancet Oncol. 2016;17:e328.

Slide credit clinicaloptions.com

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Future Directions of Most Advanced CAR T Products in Multiple Myeloma

- Race to FDA Approval in the USA
  - Global Pivotal Trial (KarMMa) of Idecabtagene vicleucel just completed enrollment
  - Legend/Janssen enrolling on pivotal trial of LCAR-B38M or JNJ-68284528
- Use Beyond the Refractory Setting
  - Trials in earlier phase of disease
    - KarMMa 3 – randomized Phase 3 of bb2121 vs SOC in pts with 2-4 priors
    - KarMMa 2 – cohort of pts with early relapse 9 (with or without ASCT), bb2121 as 2nd line
  - Trials in conjunction with ASCT/Consolidation in MRD
    - KarMMa2 – Cohort 2C upfront in pts with inadequate response to ASCT
- Dual antigen targeting to mitigate Ag escape
  - UPenn/Novartis (BCMA CART with or without CART19) [NCT03549442] – in pts responding to 1st or 2nd line therapy for high-risk MM

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Investigational Allogeneic CAR T-cells in Hematologic Malignancies

Trial	Phase	Planned N	Primary Endpoints	Treatment
NCT02746952 (CALM)	I	30	DLT, Safety	UCART19, anti-CD19 allogeneic CAR T-cell in adult R/R ALL
NCT02808442 (PALL)	I	18	Safety	UCART19, anti-CD19 allogeneic CAR T-cell in pediatric R/R ALL
NCT03939026 (ALPHA)	I/II	24	DLT, ORR	ALLO-501, anti-CD19 allogeneic CAR T-cell in R/R LBCL or FL
NCT03190278 (AMELI-01)	I	59	DLT, Safety	UCART123, anti-CD123 allogeneic CAR T-cell in R/R AML
NCT04093596 (UNIVERSAL)	I	90	DLT	ALLO-715, anti-BCMA allogeneic CAR T-cell in R/R MM
NCT04142619 (MELANI-01)	I	18	Safety	UCARTCS1A, anti-CS1 allogeneic CAR T-cell in R/R MM
NCT03971799	I/II	34	DLT, ORR	CD33CART, anti-CD33 allogeneic CAR T-cell in R/R AML

www.clinicaltrials.gov. Accessed December 12, 2020

DLT: Dose limiting toxicity

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Conclusions

- CD19 CAR T-cells are the most successful and best known CAR therapy providing durable responses in pediatric/young adult B-cell ALL, adult LBCL and MCL
- Unique toxicities of CRS and neurotoxicity may occur
  - Strategies for uniform grading to be used across clinical trials and the post-approval clinical setting recently published
- Clinical trials evaluating the use of CAR T-cells alone or in combination with other agents, in other malignancies, and versus standard of care therapies are ongoing
- Allogeneic CAR T-cell therapy may overcome barriers to current FDA approved products

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Q&A SESSION

Advances in CAR T-cell Therapy

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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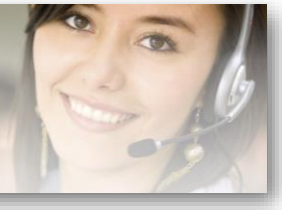

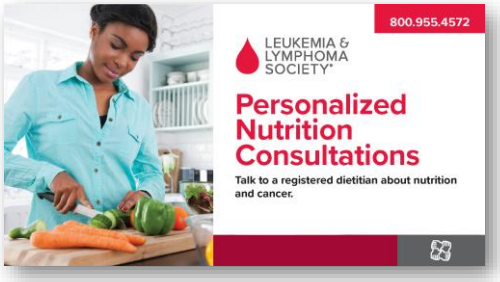

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www.LLS.org/Consult.

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Online Chats are free, live sessions, **moderated by oncology social workers**. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**.

Augmented Reality CAR T-Cell Therapy Process

Use your smartphone, tablet, or other mobile device to see the CAR T-cell therapy process in action, please visit **www.LLS.org/CART**.

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**.

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LLS EDUCATION & SUPPORT RESOURCES

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer:
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To order free materials: **www.LLS.org/Booklets**

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